DETAILED ACTION

Status of the Application

1. Claims 1-23 are pending in the Application and are currently under examination.

Information Disclosure Statement

2. The references cited in the IDSs submitted on 3/24/2008 were all considered. The references crossed out in the IDS of the 05/17/2007 were not considered since they lacked the year of publication.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6-15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-15 recite the phrase "at or about" which is a relative term which renders the claim indefinite. The phrase "at or about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term does not allow a person of ordinary skill in the art to determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-16, 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by De Meere et al. (U. S. Pat. No. 5,384,132- cited by Applicant).

De Meere et al. disclosed lyophilized gonadotropin containing preparations containing a dicarboxylic acid salt stabilizer. The particular proteins (e.g. LH, TSH, FSH, or HCG) are in admixture with, and at least partially capable of stabilization by, the particular stabilizer in lyophilized form. The preparations preferably include a non-reducing disaccharide to increase the collapse temperature of the solution to be lyophilized. Methods of making the preparations in lyophilized form and the resulting injectable preparations are also disclosed (Abstract). Follicle stimulating hormone may be at least partially isolated from natural sources, such as human urine. Recombinant follicle stimulating hormone and/or LH may be prepared by methods known in the art. FSH may be produced by recombinant DNA techniques (rFSH), either alone or in a lyophilisate with LH or HCG. Doses of FSH range from 60 to 1500, especially 75 to 225 IU per ampoule lyophilisate (col. 2, line 31-61). A container containing FSH may contain 1 to 1000 µg of FSH. Preferably, the highest reasonable amount of protein possible will be present in a container, since the greater the amount of protein present, generally the more stable the preparation. In one preferred embodiment, a

combination of FSH and LH are lyophilized together to from a preparation having therapeutic amounts of both of the selected gonadotropins (col. 3, lines 2-20). The compositions to be freeze-dried preferably contain a non-reducing sugar such as sucrose. or trehalose. The incorporation of sucrose, acts to increase the "collapse (or `shrinkage`) temperature" at which the lyophilization of the solution takes place. This increase in temperature simplifies the entire freeze-drying process. The amount of non-reducing sugar present in the solution to be lyophilized will generally be dependent upon the amount of dicarboxylic acid salt stabilizer present. Especially preferred is a solution containing 50 mg/ml sucrose which also yields an optimal lyophilisate in terms of physical characteristics (col. 4, lines 2-41). Also taught are Anti-adsorption agents that are added to the lyophilized composition to prevent adsorbance of the protein to the walls of the container in which the compositions are contained, thus preventing a possible decrease in concentration. Certain anti-adsorption agents (e.g. polysorbates) also act as "cryoprotectants" protecting the protein during the lyophilization process. Preferred anti-adsorption agents are nonionic surfactants such as Polysorbate 20, (Tween 20) (especially preferred) Polysorbate 80, (Tween 80) Polysorbate 20, NF is especially preferred. Amounts of Polysorbate 20 sufficient to form a concentration between 0.1 and 0.2 mg/ml in the ultimate solution for use are preferred. Concentrations higher than this tend to lead to oligomer formation, and thus decreased activity (col. 4, line 49 to col. 5, line 8). Another preferred stable lyophilized preparation contains, in admixture, a stabilizer such as a salt of tartaric or aspartic acid, a gonadotropin capable of stabilization by the amount of stabilizer present in the preparation, and a non-

reducing sugar. The preparation may further include disodium biphosphate in admixture with the stabilizer, protein, and non-reducing sugar. Especially preferred non-reducing sugars are trehalose and sucrose (col. 5, col. 46-55). A lyophilized composition for recombinant human FSH was made containing 75 IU rFSH, 75 IU LH, 15 mg sodium citrate, 50 mg sucrose, and 0.2 mg polysorbate 20. The preparation is reconstituted with one ml of water for injection (example VIII).

Thus all the limitation of the claims 1-16, 18 and 23 are explicitly (or implicitly-for claims 9-11) taught by De Meere et al.

7. Claims 1-17 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Skrabanja et al. ((EP 0853 945, 07/22/1998 –cited by Applicant).

Skrabanja et al. teach a liquid gonadotropin-containing formulation characterized in that the formulation comprises a gonadotropin and stabilizing amounts of a polycarboxylic acid or a salt thereof and of a thioether compound. The particular proteins (e.g. LH, TSH, FSH, or HCG) are in admixture with the particular stabilizers in aqueous solution. The preparations contain a sufficient amount of the polycarboxylic acid or a salt thereof, and a sufficient amount of the thioether compound, preferably methionine, to stabilize the protein. The preparations preferably also include a nonreducing disaccharide like sucrose, and a non-ionic in surfactant (Abstract).

The gonadotropin or gonadotropin derivatives, as used in the definition of the formulation of the present invention, are the proteins described above, e.g. follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), human chorionic gonadotropin (hCG), luteinizing hormone (LH), or derivatives, or analogs, and mixtures

thereof, with or without other protein components. The gonadotropin may be isolated from natural sources, e.g. from human urine, or the gonadotropin may be prepared in a (bio)synthetic way, by recombinant DNA techniques. The most preferred gonadotropin is FSH produced by recombinant DNA techniques (recFSH), either alone or in admixture with LH. FSH purified from natural sources is generally only partially purified. In a preferred embodiment of the invention the liquid gonadotropin containing formulation comprises as stabilizers a sufficient amount of a citric acid salt, preferably sodium citrate and a sufficient amount of the thioether compound methionine. When sodium citrate and methionine are the selected stabilizers in a liquid formulation according to the invention a suitable concentration of sodium citrate is 25-100 mM and a suitable concentration of methionine is 1-10 mM. It has been found that the incorporation of a nonreducing disaccharide, such as sucrose into a formulation, and a thioether compound as stabilizers, further increases the stability of the gonadotropin in the liquid formulation. Sucrose is the preferred disaccharide in formulations according to the invention. A concentration of sucrose of approximately 25-300 mM is a suitable amount. The formulation disclosed by Skrabanja et al. preferably also comprises one or more nonionic surfactants that act as anti-adsorption agents and prevent the loss of the gonadotropin as a result of adsorption of the protein to the walls of the container in which the formulations are kept. The addition of an anti-adsorption agent to the formulations is especially required when the formulations comprise a recombinant gonadotropin in low concentrations. Preferred nonionic surfactants are Polysorbate 20, (Tween 20) or Polysorbate 80 (Tween 80). Amounts of Polysorbate 20 sufficient to form

a concentration between about 0.1 and 0.2 mg/ml in the ultimate formulation for use are preferred. In one preferred embodiment, a combination of FSH and LH are dissolved together to from a formulation having therapeutic amounts of both of the selected gonadotropins. For FSH, useful doses range from about 25 to 1500 International Units (IU), especially 50-225. Approximately 75 IU is considered a therapeutic amount. Injections ranging from 20 to 225 international units LH have been used. The liquid gonadotropin containing formulations of the invention can be freeze-dried, if desired (p3, line 32 to p. 5, line 21: claims 1-15).

Thus the limitations of the claims 1-17 and 23 are anticipated by Skrabanja et al.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claim 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Meere et al. (U. S. Pat. No. 5,384,132) in view of Skrabanja et al. ((EP 0853 945, 07/22/1998).

The claims are drawn to a freeze dried formulation comprising the following ingredients: rFSH, rLH, Tween 20, sucrose, methionine, and a phosphate buffer. More specifically, the freeze dried formulation comprises 12.0 µg of recombinant FSH, 3.7 µg of recombinant LH, 30.0 mg of sucrose, 0.45 mg of NaH_2PO_4 H20, 1.11 mg of Na_2HPO_4 $2H_2O$, 0.05 mg of Tween 20 and 0.1 mg of L- methionine.

As presented supra, De Meere et al. teach all the elements of the formulations less the methionine.

Skrabanja et al. (see above), also teaches all the elements of the combination but the phosphate buffer.

The level of skill in the art at the time that the invention was made was very high, since formulations containing gonadotropins were previously known and used world wide. Adjusting the actual quantities of the ingredient it was therefore considered routine in the art. Therefore it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to combine the teachings of De Meere et al. and Skrabanja et al. to optimize the quantities with a reasonable expectation of success. The motivation is always present for a person of ordinary skill in the art to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

11. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Meere et al. (U. S. Pat. No. 5,384,132) in view of Franks et al. (WO/2000/067778, 11/16/2000).

The claims are drawn to an article of manufacture comprising- a first container filled with a freeze dried formulation comprising a follicle-stimulating hormone (FSH) or a variant thereof; a luteinizing hormone (LH) or a variant thereof; and, at least one surfactant selected from the group consisting of including Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), and Tween 80 (polyoxyethylene (20) sorbitan monooleate); and a second container that comprises a solvent for reconstitution, which may be water.

The teachings of De Meere et al. were presented supra and do not contain, explicitly two containers.

Franks et al. teach the use of gonadotropins in the treatment of anovulatory women (p.1 , lines 1-2). FSH and/or a biologically-active analogue thereof may be used in the production of the medicament. The IU ratio of LH to FSH is preferably in the range of from 1.5: 1 to 20: 1. More preferably, the ratio is in the range from 1.5:1 to 10:1. A particularly preferred daily dose for such a medicament is 375 IU of r-hLH and 37.5 IU of r-hFSH. (p.7, lines 6-19). Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostatics and solutes which render the formulation isotonic with the blood of the intended recipient; aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The

formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use p. 9, lines 5-15).

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to have used the freeze dried formulations of De Meere et al. in the containers of Franks et al. with a reasonable expectation of success since the teachings of Franks are representative of the state of the art in gonadotropin formulations. The motivation to do so is suggested by Franks et al.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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